Public Health Goal for
COPPER
in Drinking Water

Prepared by

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Drinking Water Public Health Goal of the
Office of Environmental Health Hazard Assessment

This Public Health Goal (PHG) technical support document provides information on health effects from contaminants in drinking water. The PHG describes concentrations of contaminants at which adverse health effects would not be expected to occur, even over a lifetime of exposure. PHGs are developed for chemical contaminants based on the best available toxicological data in the scientific literature. These documents and the analyses contained in them provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime.

The California Safe Drinking Water Act of 1996 (amended Health and Safety Code, Section 116365) requires the Office of Environmental Health Hazard Assessment (OEHHA) to adopt PHGs for contaminants in drinking water based exclusively on public health considerations. The Act requires OEHHA to adopt PHGs that meet the following criteria:

1. PHGs for acutely toxic substances shall be set at levels at which scientific evidence indicates that no known or anticipated adverse effects on health will occur, plus an adequate margin-of-safety.
2. PHGs for carcinogens or other substances which can cause chronic disease shall be based solely on health effects without regard to cost impacts and shall be set at levels which OEHHA has determined do not pose any significant risk to health.
3. To the extent the information is available, OEHHA shall consider possible synergistic effects resulting from exposure to two or more contaminants.
4. OEHHA shall consider the existence of groups in the population that are more susceptible to adverse effects of the contaminants than a normal healthy adult.
5. OEHHA shall consider the contaminant exposure and body burden levels that alter physiological function or structure in a manner that may significantly increase the risk of illness.
6. In cases of scientific ambiguity, OEHHA shall use criteria most protective of public health and shall incorporate uncertainty factors of noncarcinogenic substances for which scientific research indicates a safe dose-response threshold.
7. In cases where scientific evidence demonstrates that a safe dose-response threshold for a contaminant exists, then the PHG should be set at that threshold.
8. The PHG may be set at zero if necessary to satisfy the requirements listed above.
9. OEHHA shall consider exposure to contaminants in media other than drinking water, including food and air and the resulting body burden.
10. PHGs adopted by OEHHA shall be reviewed periodically and revised as necessary based on the availability of new scientific data.

PHGs adopted by OEHHA are for use by the California Department of Health Services (DHS) in establishing primary drinking water standards (State Maximum Contaminant Levels, or MCLs). Whereas PHGs are to be based solely on scientific and public health considerations without regard to economic cost considerations, drinking water standards adopted by DHS are to consider economic factors and technical feasibility. For this reason PHGs are only one part of the information used by DHS for establishing drinking water standards. PHGs established by

OEHHA exert no regulatory burden and represent only non-mandatory goals. By federal law, MCLs established by DHS must be at least as stringent as the federal MCL if one exists.

PHG documents are developed for technical assistance to DHS, but may also benefit federal, state and local public health officials. While the PHGs are calculated for single chemicals only, they may, if the information is available, address hazards associated with the interactions of contaminants in mixtures. Further, PHGs are derived for drinking water only and are not to be utilized as target levels for the contamination of environmental waters where additional concerns of bioaccumulation in fish and shellfish may pertain. Often environmental water contaminant criteria are more stringent than drinking water PHGs, to account for human exposures to a single chemical in multiple environmental media and from bioconcentration by plants and animals in the food chain.

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SUMMARY

A Public Health Goal (PHG) of 170 ppb is developed for copper in drinking water. Copper does not appear to be carcinogenic in animals or humans, therefore the PHG is based on noncarcinogenic effects. The PHG is based on gastrointestinal effects in children, the sensitive group for this chemical. In one case report of a Vermont family that consumed drinking water with a copper concentration of 7.8 mg/L, a seven-year-old girl experienced abdominal pain and a five-year-old girl experienced episodes of vomiting and abdominal pain after drinking the water. To calculate the lowest-observed-adverse-effect-level (LOAEL) the water consumption of the two girls was estimated at one liter per day. An uncertainty factor of 10 was employed to extrapolate from an LOAEL to a no-observed-adverse-effect-level (NOAEL), and a relative source contribution of 80% was assumed. Based on these assumptions, OEHHA calculates a PHG of 0.17 mg/L (170 ppb) for copper in drinking water.

INTRODUCTION

The purpose of this document is to develop a PHG for copper in drinking water. Copper may be present in source water or may enter tap water in the distribution system of the individual household. Tap water is used for drinking directly and also for the preparation of foods and beverages.

Copper is an essential nutrient, but it is toxic at higher intake levels. Children under 10 years of age are particularly susceptible to copper toxicity (Spitalny *et al.*, 1984; ATSDR, 1990; Mueller-Hoecher *et al.*, 1988; Klein *et al.*, 1991). As a required element, copper is incorporated into a number of proteins, such as cytochrome oxidase, lysyl oxidase and superoxide dismutase. Copper is essential for hemoglobin synthesis, carbohydrate metabolism, catecholamine biosynthesis and cross-linking of collagen, elastin and hair keratin (Solomons, 1985; ATSDR, 1990). Reports of copper intoxication in humans most often arise from accidental poisoning or suicide attempts (Akintowa, *et al.*, 1989; ATSDR, 1990).

Copper intoxication from the consumption of water containing high copper concentrations is uncommon. Symptoms of mild copper poisoning from ingestion of contaminated water are nausea, abdominal cramps, diarrhea, vomiting, dizziness and headaches. More serious cases involving hepatic and renal necrosis, coma and death have been reported as "Indian Childhood Cirrhosis" (ICC), a condition affecting primarily children under five years of age mainly in the Indian subcontinent (Sethi, *et al.*, 1993). It is generally believed that milk or water stored in brass or copper containers lead to increased dietary copper in these children (National Research Council, 1977; McClain and Shedlofsky, 1988; Lee *et al.*, 1989; Sethi *et al.*, 1993).

In this document we evaluate the available data on the toxicity of copper by the oral route, particularly toxic effects that may result from the ingestion of drinking water with high levels of dissolved copper. To determine a safe level for copper in drinking water, sensitive groups are identified and considered, and studies which can be used to identify safe levels are reviewed and evaluated.

CHEMICAL PROFILE

Copper is a naturally occurring metal with an atomic number of 29, and an average atomic weight of 63.54. The two naturally occurring stable isotopes are ^{63}Cu and ^{65}Cu, occurring in a ratio of approximately 7:3. There are two radioactive isotopes of copper, ^{64}Cu and ^{67}Cu, which have been useful for clinical and experimental purposes (Marceau *et al.*, 1970; Strickland *et al.*, 1972).

Copper is a metallic element with a bright, lustrous reddish color. It is malleable, ductile and an excellent conductor of heat or electricity. The melting point of copper is 1,083°C. The boiling point is 2,336°C. The specific gravity of copper is 8.94.

Copper exists in two valence states: monovalent (cuprous) and divalent (cupric). Copper is found in pure metallic form, or as a component of many minerals, including sulfides, oxides and carbonates. Pure copper can be obtained from these minerals by smelting, leaching or electrolysis. The copper salt most frequently used in toxicological experiments is cupric sulfate ($CuSO_4$).

PRODUCTION AND USE

Copper may have been the first metal that human beings smelted and used for manufacturing implements. The manufacture of copper tools and weapons ended the neolithic age (or late stone age) and eventually led to the bronze age when humans learned to alloy copper with tin and other metals.

Unalloyed copper is still used to make coins, electrical wiring, casings for ammunition and water pipes. Copper has excellent electrical and heat conductivity which makes it useful for electrical wires and for cooking applications. The ductility of copper makes it useful for water pipes that can be bent to fit particular applications.

Bronze (copper alloyed chiefly with tin) is used in a wide variety of applications. Brass (copper alloyed with zinc) is an attractive metal for decorative purposes such as rails and doorknobs, and is used in making musical instruments.

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

Because copper is a component of many naturally occurring minerals, and because of its extensive use in industry, copper is very widespread in the human environment. Copper occurs in virtually all media that humans contact including air, water and soil (ATSDR, 1990; Nriagu, 1990).

Air

Copper emitted into the air from natural sources amounts to 28 thousand tons annually, whereas anthropogenic sources contribute another 35 thousand tons (Nriagu and Pacyna, 1988). Natural sources include wind-blown dust, volcanic activity and spray from ocean waves. The anthropogenic sources are the mining, refining, smelting and incineration of copper and related metals that are mixed or alloyed with copper in the ores and in the processed forms (ATSDR, 1990). The concentrations of copper detected in air samples from "remote areas" range widely from a high of 110 ng/m^3 to a low of 0.014 ng/m^3 as reported by Wiersma and Davidson (1986).

Soil

Copper is discharged to land from sewage treatment plants, as well as from mining and industry. It is estimated that 97% of copper released to the environment is deposited on land (ATSDR, 1990). Copper in soil can leach to ground water, thus contaminating drinking water sources.

Water

Well water has a highly variable copper content that is dependent on the soil and the underlying water table (Lonnerdal, 1996). Additional copper is added to water due to leaching from the distribution system as drinking water is carried from the water treatment plant to the tap (Lonnerdal, 1996; Sharrett *et al.*, 1982). The leaching of copper into drinking water in the home distribution system is greater if the water is slightly acidic or very soft (Lonnerdal, 1996; Sharrett *et al.*, 1982). The use of copper sulfate for water treatment may also add copper to drinking water in some cases. Drinking water typically contributes only about 4% to 15% (0.08 to 0.3 mg) of the adult daily nutritional requirement for copper of 2 mg/day (NRC, 1980). Childrens' nutritional requirement for copper is approximately 75% that of adults (1.5 mg/day compared to 2 mg/day, see below). If we assume that children drink approximately half as much drinking water as adults (1 liter/day compared to 2 liters/day) then for children drinking water would supply approximately 3% to 10% of the daily nutritional requirement of copper.

Food

As part of a total diet study (Pennington *et al.*, 1986), the U.S. Food and Drug Administration (FDA) estimated the daily dietary intake of copper and other essential trace elements for eight sex per age groups of the United States (U.S.) population. These estimates were based on composite samples of 234 foods purchased in 24 U.S. cities, together with earlier estimates of dietary intakes of these foods by both males and females per age groups. Table 1 displays the results of this study for copper.

Table 1. Dietary Intakes of Copper for Males and Females per Age Group

Sex/Age Group	Dietary Copper Intake (mg/day)
6-11 month old infant	0.47
2 year old child	0.58
14 to 16 year old girl	0.77
14 to 16 year old boy	1.18
25 to 30 year old woman	0.93
25 to 30 year old man	1.24
60 to 65 year old woman	0.86
60 to 65 year old man	1.17

Gibson (1994) compiled several studies and found that copper intakes in adults were approximately 1.0 to 1.5 mg/day from omnivore diets, whereas vegetarian diets provided 2.1 to 3.9 mg/day copper. Copper intakes for children were 0.8 to 1.9 mg/day, with most of the higher intakes from vegetarian diets (Gibson, 1994).

These estimated dietary intakes of copper are low, relative to the "safe and adequate" level for this nutrient (Lonnerdal, 1996). Because of limited data, the National Research Council (NRC) has not established a recommended dietary allowance (RDA) for copper (NRC, 1989). Instead, NRC has set a "safe and adequate level" of 2.0 to 3.0 mg/day for adults and adolescents, 1.0 to 2.0 mg/day for children 7 to 10 years of age and 0.5 to 1.0 mg/day for infants (NRC, 1989). The World Health Organization (WHO, 1973) recommends 80 µg/kg per day for infants. The American Academy of Pediatrics (1985) has recommended 60 µg of copper per 100 kcal in infant formulas. This would provide 0.4 mg of copper/day for an infant consuming 700 kcal/day.

The copper intake in the diet is made up of contributions from a variety of foods. Potatoes and other vegetables make the largest contribution (approximately 30%). Meat, poultry, fish and bread contribute significantly (approximately 20%). Other food groups contribute lesser amounts (Solomons, 1985; Lonnerdal, 1996). The food with the highest copper content is beef liver which contains 61 ppm copper. Because breast milk is low in copper, it can be difficult to ensure adequate copper for the infant (Solomons, 1985; Lonnerdal, 1996).

Commercial infant formulas when constituted with water contain approximately 500 to 600 µg/L of copper (based on formula on product container). This amount of copper is adequate to supply the dietary requirement for copper.

METABOLISM AND PHARMACOKINETICS

Copper probably occurs in drinking water in the form of cupric ion (Cu^{+2}) complexed with organic ligands (U.S. EPA, 1987). Although it is normally assumed that copper in water is as biologically available as the copper in food, there may be components in food that can influence the metabolism, absorption and mobilization of copper in human diets. For example, high levels of vitamin C (ascorbic acid) adversely affect the absorption and metabolism of copper. There appears to be an antagonistic relationship between copper and zinc absorption and transport (Cousins, 1985).

Absorption

In humans, dietary copper is absorbed from the stomach and small intestine (Cousins, 1985). In humans about 65% of an oral dose of ^{64}Cu as copper acetate was absorbed from the gastrointestinal tract (range 15 - 97%) (Weber *et al*., 1969; Strickland *et al*., 1972). Orally administered ^{64}Cu rapidly appears in the plasma (Bearn and Kunkel, 1955).

Copper absorption in the gastrointestinal tract has been studied in rats and hamsters. Absorption takes place from the stomach and duodenum in rats (Van Campen and Mitchell, 1965) and from the lower small intestine in hamsters (Crampton *et al.*, 1965). Copper absorbed from the gastrointestinal tract may be bound to amino acids or in the form of ionic copper. Copper becomes bound to metallothionein in the intestine and is released into the bloodstream as metallothionein-copper (Marceau *et al.*, 1970).

Protein source (plant or animal protein), amino acids, carbohydrates and ascorbic acid can affect copper availability (Gibson, 1994; Lonnerdal, 1996). Competition with zinc and cadmium affects copper absorption from both diet and drinking water (Davies and Campbell, 1977; Hall *et al.*, 1979). High dietary ascorbic acid interferes with absorption of copper (Smith and Bidlack, 1980). Ascorbic acid may alter the metallothionein binding site. Phytates and fiber interfere with copper

absorption by forming complexes with copper (Gibson, 1994). The amount of stored copper in humans (mainly in the liver) does not appear to affect copper absorption (Strickland *et al.*, 1972).

There do not appear to be any available studies of copper absorption in humans by inhalation. Batsura (1969) observed copper oxide in alveolar capillaries after rats were exposed to welding dust from a pure copper wire. No studies of the rate or extent of absorption of copper through intact human skin were found, but as copper can cause contact dermatitis, some absorption must occur (ATSDR, 1990). Pirot *et al.* (1996) studied the absorption of copper and zinc through human skin *in vitro*. Skin absorption is not likely to contribute significantly to total copper absorption.

Distribution

Copper is transported in the plasma bound to ceruloplasmin, albumin or amino acids (Cousins, 1985). Ceruloplasmin is a cysteine-rich glycoprotein with many free sulfhydryl groups that serve as binding points for metals. Ceruloplasmin can bind copper or zinc, but has a stronger affinity for copper (Cousins, 1985). Ceruloplasmin is synthesized on membrane-bound polyribosomes of liver parenchymal cells and secreted into the plasma. Copper that enters the portal circulation from the intestine is transported directly to the liver. Copper released from the liver is transported in the bloodstream to other organs including the kidney and brain. The synthesis of ceruloplasmin is controlled by interleukin-I via glucagon or glucocorticoid (Cousins, 1985). Circulating copper levels are elevated in pregnant women because hormonal changes associated with pregnancy stimulate ceruloplasmin synthesis (Solomons, 1985).

Metabolism and Excretion

Copper is taken up by hepatocytes from the portal circulation. Inside the hepatocytes copper is bound to metallothionein, a protein that also binds zinc, iron and mercury. Copper can be released from hepatocytes into the general circulation to be transported to other tissues, or it can be excreted from the liver in bile (Cousins, 1985). The major route of excretion is in the bile. Only a small amount is excreted in the urine (Cousins, 1985).

Physiological Functions of Copper

Because copper is an essential nutrient that has numerous physiological roles in the body, an understanding of these roles is essential for understanding the deleterious effects of copper deficiency or excess.

Copper is essential for hemoglobin synthesis and erythropoiesis (Solomons, 1985; Harris, 1997). Copper deficiency can therefore lead to anemia. Copper deficiency can likewise lead to abnormalities of myelin formation, with attendant effects on the nervous system (Solomons, 1985; Harris, 1997). Nervous system effects, including dementia have been observed in individuals with copper deficiency or excess (Solomons, 1985; Harris, 1997). Effects on catecholamine metabolism likewise are involved in nervous system abnormalities.

Other physiological functions that involve copper include: leukopoiesis, skeletal mineralization, connective tissue synthesis, melanin synthesis, oxidative phosphorylation, thermal regulation, antioxidant protection, cholesterol metabolism, immune and cardiac function, and regulation of glucose metabolism. Since all of these physiological processes involve copper, any of them can be

affected by the availability of copper in the body or in specific tissues. In general, deleterious effects may occur in any of these physiological processes due to either deficiency or excess of copper in the systems affected (Solomons, 1985; Harris, 1997).

TOXICOLOGY

Toxicological Effects in Animals

Acute Toxicity

An oral LD_{50} of 300 mg cupric sulfate/kg in rats has been reported (Siegel and Sisler, 1977). Details of the toxic effects on the rats were not reported.

Subchronic Toxicity

Rats administered a diet containing 4,000 ppm of copper (approximately 133 mg/kg-day) for one week exhibited increased mortality from anorexia, possibly resulting from taste aversion (Boyden *et al.*, 1938).

High levels of copper in the diet can lead to hepatocellular necrosis in the liver and structural damage to proximal convoluted tubules in the kidneys (Haywood, 1985). Rats administered 3,000 to 5,000 ppm of copper in the diet developed these pathological changes, but gradually adapted to the high copper diets after four to six weeks (Haywood, 1985). Adaptation involved changes in copper metabolism, and regeneration of damaged tubular epithelium in the kidneys. Regenerated epithelium is histologically different from undamaged epithelium. Rats exposed to 6,000 ppm of copper in the diet (300 mg/kg-day) were not able to adapt, and in some cases died from extensive centrilobular necrosis (Haywood, 1985).

To investigate reproductive effects of copper, Haddad *et al.* (1991) administered copper acetate in drinking water to albino Wistar rats before and during pregnancy. The water was supplemented with copper acetate increasing stepwise to a concentration of 0.185% over a period of seven weeks. Copper was deposited in the liver and kidneys of pregnant rats leading to inflammation of those organs. Examination of 11.5 day-old embryos revealed moderate retardation of growth and differentiation, especially of the neural tube. Older embryos (21.5 days) had reduced numbers of ossification centers in the vertebrae, sternum and phalanges of the forelimbs and hindlimbs when compared to untreated controls. Minimal growth retardation was seen in newborn rats. The authors concluded that loading maternal rats with copper at tissue levels approximately 10-fold above normal was toxic to the dams (inflammation of liver and kidneys) but resulted in only minor growth retardation to the offspring.

In a National Toxicology Program (NTP) study (1993), rats and mice were exposed to cupric sulfate in drinking water (free drinking) at concentrations up to 30,000 ppm for 15 days. The only compound-related toxic effect observed was an increase in the size and number of cytoplasmic protein droplets in the epithelium of the renal proximal convoluted tubules in male rats of the 300

and 1,000 ppm groups (NTP, 1993). The absence of effects at the highest exposure level (30,000 ppm) may have been due to taste aversion.

The above-mentioned NTP study also included a two-week feeding study with concentrations of cupric sulfate in feed ranging from 1,000 to 16,000 ppm (NTP, 1993). In this study hyperplasia and hyperkeratosis of the squamous epithelium of the limiting ridge of the forestomach was observed in rats and mice of both sexes in all dosage groups (NTP, 1993). Periportal to midzonal inflammation of the liver occurred in rats of the 8,000 and 16,000 ppm groups. Both male and female rats in the 8,000 and 16,000 ppm groups showed depletion of hematopoietic cells in the bone marrow and spleen. Male and female rats in the 4,000, 8,000 and 16,000 ppm groups exhibited increased protein droplets in the epithelia of the renal cortical tubules (NTP, 1993).

Chronic Toxicity

Noncarcinogenic Effects

Pigs administered to 250 ppm copper in their diet had significantly reduced body weight gain apparently resulting from reduced food consumption. They also exhibited reduced hemoglobin, hematocrit, mean cell volume, mean cell hemoglobin and plasma and liver iron levels (Gipp *et al.*, 1973). Sheep are more sensitive to copper toxicity than are pigs. As little as 10 to 15 ppm copper in the diet of sheep resulted in hemolytic anemia (Booth and McDonald, 1982). In the case of copper poisoning in sheep there is a long delay period of several months during which copper accumulates in the liver lysosomes. When the capacity of the sheep liver to store copper is exceeded, the copper is released and brings about the toxic effects.

Excess copper has been reported to disrupt a number of processes in the central nervous system (De Vries *et al.*, 1986). Copper administered to rats acted on brain synapses to inhibit uptake of monoamines including noradrenaline and dopamine (De Vries *et al.*, 1986).

Copper and copper complexes have anti-inflammatory, antiulcerogenic and anticarcinogenic effects. They are sometimes administered to patients for these effects (Sorenson, 1983). However, excess copper may have deleterious effects on the immune system as evidenced by increased severity of infections in chickens (Hill, 1980) and mice (Vaughn and Winberg, 1978).

To further investigate the effect of excess copper on the immune system, Pocino *et al.* (1991) investigated the proliferative response to T and B cell mitogens, and the delayed-type hypersensitivity (DTH) response in mice exposed to excess copper (50, 100, 200 or 300 ppm) in drinking water (Pocino *et al.*, 1991). They found the DTH response was significantly inhibited in mice exposed to 100 ppm copper; and the proliferative response to T and B cell mitogens was significantly inhibited in animals exposed to 200 ppm copper.

In an NTP study (1993) rats and mice were administered cupric sulfate in the diet ranging from 500 to 8,000 ppm for 13 weeks. In this study rats in the three highest dose groups exhibited hyperplasia and hyperkeratosis of the forestomach, inflammation of the liver and increases in the number and size of protein droplets in the epithelium of the proximal convoluted tubules. Both female and male mice receiving 4,000 ppm cupric sulfate and higher in the 13-week study exhibited increased hyperplasia and hyperkeratosis of the squamous mucosa on the limiting ridge of the forestomach (NTP, 1993).

Carcinogenic Effects

In a study published in 1968, Bionetics Research Labs tested copper hydroxyquinoline for carcinogenic effect in B6C3F1 and B6AKF1 mice. Groups of 18 male and 18 female seven-day-old mice were given daily by gavage 1,000 mg copper hydroxyquinoline per kg of body weight (180.6 mg Cu/kg bw) suspended in 0.5% gelatin until they were 23 days old, after which they were given 2,800 ppm (505.6 ppm Cu) in their feed for 50 additional weeks. No statistically significant increases in tumor incidence were observed in the treated animals (U.S. EPA, 1994).

In the same study, 28-day-old mice of both strains and sexes were given a single injection of 1,000 mg copper hydroxyquinoline/kg (180.6 mg Cu/kg) suspended in 0.5% gelatin. Control mice were given injections of only the gelatin. After 50 days, the male B6C3F1 mice had an increased incidence of reticulum cell sarcomas compared with the controls. No tumors were observed in the treated male B6AKF1 mice, and a low incidence of reticulum cell sarcomas was observed in treated female mice of both strains.

In experiments intended to determine the active agents in nickel refinery dust, Wistar rats (two and three months old) were injected intramuscularly in the thighs with 20 mg of cupric oxide (16 mg Cu), cupric sulfide (13.3 mg Cu), or cuprous sulfide (16 mg Cu) (Gilman, 1962). After 20 months, no injection site tumors were observed in the animals that had been injected with the copper compounds. "Miscellaneous tumors" (mammary fibroadenomas and a reticulocytoma) were detected at very low incidence in rats that received cupric sulfide (2/30) and cuprous sulfide (1/30).

Rats and mice exposed to copper in the diet at concentrations of 5 to 1,000 mg/kg body weight exhibited no significant increases in tumor frequencies (Kamamoto *et al*. 1973; Green *et al*. 1987). Copper inhibited the carcinogenic effect of DL-ethionine in rat livers (Kamamoto *et al.*, 1973).

The U.S. Environmental Protection Agency (U.S. EPA) reviewed the published data and concluded that there is inadequate evidence to conclude that copper is carcinogenic in animals (IRIS, 1994). We concur with this conclusion.

Genotoxic and Cytotoxic Effects

Dose-related mutagenesis in a reverse mutation assay in *Escherichia coli* exposed to 2 to 10 ppm cupric sulfate have been reported by Demerec *et al.* (1951). A more recent study by Moriya *et al.* (1983) resulted in no increase in mutations in *E. coli* or *Salmonella typhimurium* strains TA98, TA1535, TA1537 and TA1538 incubated with up to 5 mg copper quinolinate per plate or in *S. typhimurium* strains TA98 and TA100 incubated with up to 5 mg cupric sulfate per plate. Negative results were also obtained with cupric sulfate or cupric chloride in assays with *Saccharomyces cervisiae* (Singh, 1983) and *Bacillus subtilis* (Nishioka, 1975; Matsui, 1980; Kanematsu *et al.*, 1980).

Sirover and Loeb (1976) investigated the effect of metal salts, including copper salts, on the fidelity of DNA transcription from poly(C) and other templates in an *in vitro* system that included DNA polymerase from avian myeloblastosis virus. They found that the copper salts tested decreased the fidelity of transcription by more than 30%. Induction of chromosomal aberrations has been reported in isolated rat hepatocytes incubated with cupric sulfate (Sina *et al.*, 1983).

Cuprous sulfide and cupric sulfate enhanced cell transformation in Syrian hamster embryo cells infected with simian adenovirus (Casto *et al.*, 1979).

Kim *et al.* (1994) studied the mechanism of cellular copper toxicity in Long-Evans Cinnamon (LEC) mutant rats. They found that a cellular event required for the initiation of DNA synthesis upon growth stimulation is impaired by copper cytotoxicity.

Injection of inbred Swiss Mice with doses of copper sulfate ranging from 5 to 20 mg/kg resulted in dose-dependent statistically significant increases in chromosomal aberrations, micronuclei and sperm abnormalities (Bhunya and Pati, 1987). Thus, there is *in vivo* as well as *in vitro* evidence for the genotoxicity of copper salts (ATSDR, 1990).

Toxicological Effects in Humans

Acute Toxicity

Death from ingestion of copper salts has been reported after as little as 2 grams of cupric sulfate (Stein *et al.*, 1976). Immediate deaths are caused by central nervous system (CNS) depression and shock. Later deaths (after 24 hours) are caused by hepatic and renal failure (Jantsch *et al.*, 1985).

Deaths have also been reported as the result of the use of water with dissolved cupric sulfate in religious rituals (Akintowa *et al.*, 1989). The poisoned individuals ingested approximately 20 grams each of cupric sulfate dissolved in "spiritual water" at a concentration of 100 g/L. There were four fatal cases. The symptoms exhibited by these individuals included toxic psychosis, profound greenish vomiting, hemolytic anemia and jaundice. Death occurred within eight days after ingestion for all four victims.

A group of military nurses attending a party consumed a cocktail that had become contaminated with copper from the corroded vessel in which the beverage was prepared and stored (Wyllie, 1957). The nurses who consumed this cocktail reported abdominal cramps, nausea, vomiting, dizziness and headache. The lowest amount of copper that gave rise to these symptoms was determined to be 5.3 mg (Wyllie, 1957). This was used as an LOAEL by U.S. EPA in setting the Maximum Contaminant Level Goal (MCLG) for copper (U.S. EPA, 1991).

Twenty workers experienced gastrointestinal distress and other symptoms of copper poisoning as a result of drinking morning tea prepared with water from an old "geyser" made of sheet copper. The internal surfaces of the geyser were not lined with tin as they usually are in this type of appliance. Leftover tea prepared in this geyser had a copper content of 30 ppm (30 mg/L). It is likely that the tea consumed by the workers had an even higher copper content (Nicholas, 1968).

Copper has been shown to be involved in the metabolism of vasoneuractive amines such as serotonin, tyramine and the catecholamines (Harrison, 1986). Harrison presents evidence to show that the ingestion of foods with high copper content (e.g., chocolate) or which facilitate absorption of copper (e.g., citrus fruits) may trigger migrane headaches particularly in individuals with abnormal copper metabolism due to low levels of ceruloplasmin, transferrin or albumin. This paper presents no data which could be used to estimate a dose-response relationship, but the author recommends that individuals subject to migraines avoid foods high in copper.

Chronic Effects

Noncarcinogenic Effects

Chronic effects of copper poisoning include respiratory symptoms, gastrointestinal disturbances, nervous dysfunction, dermal and hematological changes and hepatomegaly. Atrophic changes in the mucous membranes of the nose have also been noted in those chronically exposed to copper dust in the air.

Spitalny *et al.* (1984) reported on a Vermont family who consumed water contaminated with 7.8 mg/L copper. Three of four members of this family reported recurrent episodes of gastrointestinal problems including vomiting and abdominal pain. The seven-year-old girl experienced periumbilical abdominal pains 5 to 10 minutes after drinking water and orange juice in the morning. The five-year-old girl had vomiting episodes with abdominal pain after drinking the water. The father also experienced periods of emesis and abdominal pain after drinking water drawn from the kitchen faucet. This family was exposed to excess copper in their drinking water in addition to dietary exposure as described previously under 'Environmental Occurrence and Human Exposure." The investigators did not attempt to estimate the amount of copper this family received in their diet. In the absence of specific data on this family, the simplest assumption would be that their dietary exposure was not unusual. In deriving an LOAEL from this report, it should be considered that the drinking water exposure is in addition to dietary exposure and the toxicological effects might have been cumulative; no data are available to quantify any cumulative exposure or toxicity. Therefore, any LOAEL derived from this report would be for the drinking water exposure added to a baseline dietary exposure.

The Wisconsin Division of Health reported investigations of five cases of individuals who ingested drinking water with copper above the federal action level of 1.3 mg/L (Knobeloch *et al.*, 1994). Based on these cases they concluded that drinking water with elevated copper levels may be a relatively common cause of diarrhea, abdominal cramps and nausea.

Several population subgroups may be considered more susceptible to toxic effects of copper exposure (ATSDR, 1990):

1. Individuals with Wilson's Disease (McClain and Shedlofsky, 1988; Lee *et al.*, 1989), an autosomal recessive disorder causing hepatocellular degeneration due to an excess retention of hepatic copper and impaired biliary copper excretion. This occurs in about 1 in 200,000 individuals (NRC, 1977).

2. Individuals with Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency (Beutler, 1991). An inherited deficiency of this enzyme occurs in many individuals of Chinese, Greek, Italian and American and African black populations. It has been estimated that 13% of the male American black population has a hereditary deficiency of red blood cell G6PD. This enzyme is essential to the formation of NADPH, which produces reduced glutathione (GSH), the major intracellular thiol active in protecting against free radicals and oxidizing agents. There is controversy as to whether these individuals represent a sensitive population.

3. Extracorporeal dialysis patients. Kidney dialysis patients exposed to excess copper in the dialysate can suffer acute hemolytic anemia (Williams, 1982).

4. Infants and children. Infants and children up to age 10 are susceptible to the toxic effects of copper as evidenced by the incidence of ICC and reports of adverse effects in children drinking water containing low levels of copper (ATSDR, 1990; Spitalny *et al.*, 1984; Mueller-Hoecker, *et al.*, 1988). This is because the fetus and newborn have elevated hepatic copper levels and since their homeostatic mechanisms are not fully developed at birth, they may not be able to cope with excess copper exposure (Klein, *et al.*, 1991). Conversely, infants (especially premature infants) may be at risk for copper deficiencies because of "low prenatal stores" and because breast milk is low in copper (Solomons, 1985; Lonnerdal, 1996). As with other metals, copper intake in the infant should be adequate but not excessive (Solomons, 1985; Lonnerdal, 1996).

Carcinogenic Effects

Epidemiological studies have not established a positive correlation between high copper exposure and cancer. The increased incidence of lung cancer reported among workers in copper ore mines was probably due to contaminating arsenic compounds (U.S.EPA, 1987). There have been some geographical studies comparing cancer incidences in areas with high or low copper, but these studies considered together are inconclusive (U.S.EPA, 1987).

Higher copper levels have been found in tumor tissues at many sites. However, this may be a consequence rather than a cause of the disease. Cancer may increase copper absorption into the tissue.

DOSE-RESPONSE ASSESSMENT

Noncarcinogenic Effects

The most sensitive endpoint for copper is gastrointestinal effects in children. There are very limited data available for assessing the dose-response relationship for this effect. Gastrointestinal effects in children have been reported for drinking water with a copper concentration of 7.8 mg/L (Spitalny *et al.*, 1984). There have been no reports of gastrointestinal effects in children or adults for drinking water sources with copper concentrations lower than this (ATSDR, 1990).

In a Vermont family who consumed drinking water contaminated with 7.8 mg/L copper, three of four family members reported recurrent episodes of gastrointestinal problems including vomiting and abdominal pain (Spitalny *et al.*, 1984). The seven-year-old girl experienced periumbilical abdominal pains 5 to 10 minutes after drinking water and orange juice in the morning. The five-year-old girl had vomiting episodes with abdominal pain after drinking the water.

The following assumptions are made in the calculation of the LOAEL:

1. The amount of fluid consumed by the seven-year-old child was one "cup" of orange juice and one cup of water. Assume that one cup is 6 ounces. Six ounces equals 177 mL.

2. The five-year-old consumed one cup of water (6 ounces).

3. The orange juice was made from concentrate using tap water.

Amount of copper causing gastrointestinal distress to the seven-year-old child:

$$[Cu] \quad = \quad 7.8 \text{ mg/L} \times 177 \text{ mL/cup} \times 2 \text{ cups} \div 1,000 \text{ mL/L}$$
$$= \quad 2.8 \text{ mg}$$

This single oral dose can be considered equivalent to an LOAEL (i.e., 2.8 mg/day). Similarly, the LOAEL calculated for the five-year-old child is 1.4 mg.

Carcinogenic Effects

There is inadequate evidence to conclude that copper is carcinogenic in animals (IRIS, 1994). Epidemiological studies of potential carcinogenic effects in humans are inconclusive (U.S. EPA, 1987). Given the lack of data, no dose-response assessment can be made.

CALCULATION OF PHG

Calculation of the PHG for copper is be based on children as a sensitive group. This does not include children with inherited abnormalities in copper metabolism (see page 11) because such individuals are rare (about 1 in 200,000 individuals; NRC, 1977). Attempting to protect such individuals by means of a water standard would be impractical, and therefore children with inherited abnormalities should be under the care of physicians who can use more effective means of protecting them.

The following general equation for noncarcinogenic endpoints is used for calculating a public health-protective concentration (C) for copper (in mg/L) in drinking water:

$$C \quad = \quad \frac{\text{LOAEL x RSC}}{\text{UF x L/day}} \quad = \quad \text{mg/L}$$

where,

LOAEL	=	Lowest-observed-adverse-effect-level (2.8 mg/day or 1.4 mg/day from drinking water exposure in addition to baseline dietary exposure)
L/day	=	Volume of daily water consumption (1.0 L/day for child)
UF	=	Uncertainty factor (10-fold) to accout for human variability
RSC	=	Relative source contribution of 80% (0.8) based predominantly on the assumption that all copper exposure in excess of the diet would be from drinking water.

The LOAEL derived from Spitalny *et al.* (1984) is for the drinking water component of the total copper exposure. Total exposure would include exposure from diet (see Table 1). Because the LOAEL included normal dietary intake of copper, the relative source contribution (RSC) is 80% (0.8) for the purpose of this calculation. An RSC of 80% is the highest value assumed by the Office of Environmental Health Hazard Assessment (OEHHA) in deriving PHGs.

In the calculation of a public health-protective concentration (C) for copper, a UF of 10 is used as the composite uncertainty factor to account for three areas of uncertainty, including the conversion of an LOAEL to an NOAEL, using subchronic rather than chronic data because of limited data and to account for human variability. It has been suggested that different areas of uncertainty may be combined in a single factor (Dourson *et al.*, 1996). A 10-fold uncertainty factor is appropriate because these areas of uncertainty are quite significant. A higher uncertainty factor would not be appropriate for these data because it would result in a PHG which would be unduly restrictive of an element which is an essential nutrient.

For the seven-year-old child:

$$C = \frac{2.8 \text{ mg/day} \times 0.8}{10 \times 1.0 \text{ L/day}} = 0.224 \text{ mg/L}$$

For the five-year-old child:

$$C = \frac{1.4 \text{ mg/day} \times 0.8}{10 \times 1.0 \text{ L/day}} = 0.112 \text{ mg/L}$$

The average calculated public health-protective concentration (C) would be approximately 0.168 mg/L which can be rounded to 0.17 mg/L (170 ppb). Therefore, the calculated PHG for copper is 170 ppb in drinking water.

RISK CHARACTERIZATION

This PHG is based on a report by Spitalny *et al.* (1984) of gastrointestinal effects of copper in children. The LOAELs from this report were 1.4 mg/day for a five-year-old child, and 2.8 mg/day for a seven-year-old child. Another report of acute exposure to adults (Wyllie, 1957) yielded an LOAEL of 5.3 mg/day. Considering the difference in body weight (and other factors) between adults and children, the two reports produced comparable estimates of the LOAEL for gastrointestinal effects.

The Spitalny *et al.* (1984) report was chosen because it is the best and most directly applicable report on human exposures. It directly address the sensitive population group (children). However, there are four main areas of uncertainty that should be considered in using the data from the Spitalny *et al.* (1984) report to derive a PHG.

1. The report provides an LOAEL, not an NOAEL.

2. The database consists of only two individual children, a very limited sample of the total population of children. There may be considerable variability among children with respect to sensitivity to the gastrointestinal effects of copper.

3. The report describes episodes that occurred within a context of chronic exposure. We do not know for how long the children were exposed to high levels of copper in their drinking water. The gastrointestinal effects occurred shortly after drinking water or orange juice. The total time course of exposure is not precisely defined.

4. The report provides no information about dietary exposure to copper in these children. We can only assume that dietary exposure was normal (i.e., in the range shown in Table 1). According to Table 1, children in this age range would receive 0.6 to 0.8 mg/day of copper from their diet. For children, drinking water normally contributes 3% to 10% of the daily nutritional requirement for copper. This PHG would allow an additional 0.17 mg/day from drinking water. Drinking water could thus contribute up to approximately 12% of the nutritional requirement for copper. The PHG is low enough to protect against the toxic effects of copper (with a margin-of-safety) without being so low as to conflict with the dietary requirement for copper. Most of the nutritional requirement for copper normally would come from the diet.

OTHER STANDARDS AND REGULATORY LEVELS

WHO (1982) has a provisional limit of 2 mg/L for copper in tap water. The Occupational Safety and Health Administration (OSHA) has set air standards for copper. The standard for copper fume is 0.1 mg/m^3. The standard for mists and dusts is 1.0 mg/m^3 (29 CFR 1910.1000).

U.S. EPA has adopted an MCLG of 1.3 mg/L for copper in drinking water (U.S. EPA, 1991). U.S. EPA has set a secondary maximum contaminant level (SMCL) for copper in drinking water of 1.0 mg/L (40 CFR 143). U.S. EPA has set an "action level" for copper of 1,300 ppb (Title 22 CCR section 64672.3).

Copper in drinking water is regulated by the lead and copper rule, a Federal and State drinking water standard (Title 22 CCR section 64672.3) that specifies requirements for copper in drinking water systems (measured at the customers' taps). The action level is used to determine the treatment requirements that a water system must complete. The action level for copper is exceeded if the concentration of copper in more than 10 percent of the tap water samples collected during any monitoring period (conducted in accordance with 22 CCR sections 64682 to 64685) is greater than 1,300 ppb. Failure to comply with the applicable requirements for lead and copper is a violation of primary drinking water standards for these substances (22 CCR Chapter 17.5). Therefore, for all practical purposes the standard described in the lead and copper rule is an MCL.

The American College of Government and Industrial Hygienists (ACGIH) has set air standards (time-weighted average, threshold limit value) for copper fume of 0.2 mg/m^3 and 1.0 mg/m^3 for dusts and mists (ACGIH, 1988). The National Institute of Occupational Safety and Health (NIOSH) has set occupational exposure limits of 0.1 mg/m^3 for copper fume and 1.0 mg/m^3 for mist (NIOSH, 1985).

A group of state toxicologists (Sidhu *et al.*, 1995) have proposed a drinking water standard for copper of 0.3 mg/L, based on the same human study on which U.S. EPA based their standard, but employing a larger uncertainty factor. They argue that a more protective standard is needed because of the susceptibility of children under 10 years of age. We have chosen the report of Spitalny *et al.* (1984) because it represents data on the sensitive subgroup that we are trying to protect, and because the data appear to be more reliable. The standard we have calculated offers

an additional 1.8-fold margin of safety and is therefore slightly more health protective than that of Sidhu *et al.* (1995).

Various states have set guidelines for drinking water concentrations and acceptable ambient air concentrations. These are shown in Tables 3 and 4 (ATSDR, 1990).

Table 2. State Drinking Water Guidelines

State	Drinking Water Guideline
Kansas	1.0 mg/L
Minnesota	1.3 mg/L
Rhode Island	1.0 mg/L

Table 3. State Acceptable Ambient Air Concentrations

State	Ambient Air Concentration Guideline
Connecticut	2.0 $\mu g/m^3$, 8 hour
Florida	4.0 $\mu g/m^3$, 8 hour
Montanna	1.57 $\mu g/m^3$, 24 hour; 0.26 $\mu g/m^3$, 8 hour
North Dakota	2.0 $\mu g/m^3$, 8 hour
Nevada	5.0 $\mu g/m^3$, 8 hour
New York	20 $\mu g/m^3$, 1 year
Virginia	16 $\mu g/m^3$, 24 hour
Kentucky	100 $\mu g/m^3$, 8 hour
Massachusetts	0.54 $\mu g/m^3$, 24 hour

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